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How to Maintain Pregnancy

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1. Introduction

On some days, “how to maintain pregnancy” seems an elusive goal. In some cases, by the time practitioners recognize that a mare is demonstrating signs of preterm birth, any assistance we can provide is insufficient to allow delivery of a vigorous and healthy foal. Thus, a large component of how to maintain pregnancy is determining when to intervene.

Bosh et al (2009) described reproductive performance measures among 1011 Thoroughbred mares in central Kentucky during the 2004 mating and 2005 foaling seasons (Table 1). This study demonstrated a 12.9% pregnancy loss between day 40 of gestation and foaling.1

This is similar to fetal loss rates between 3 and 10 months gestation found in other studies.2 In comparison, the human rate of preterm births in the United States in 12.5%.3

In a review of 3527 aborted fetuses and placentas, stillborn foals or foals that died <24 hours after birth, 34% were due to fetal-placental infection or placentitis of unidentified etiology. Bacterial infection caused 628 (17.8%) of these losses. Complications of birth led to the demise of 679 (19%), congenital anomalies including contracted foals counted for 348 (10%), and no diagnosis was identified in 585 (17%) of these cases. Other causes included placental edema, premature placental separation, twins, umbilical cord anomalies, placental villous atrophy, body pregnancy, fetal diarrhea, and neoplasia. This tells us that if we can manage inflammation and infection, we are targeting approximately one-third of the problem.4

The vast majority of pregnancies will require no intervention. For anxious clients or mares at higher risk for problematic pregnancy, routine monitoring can be instituted. Case selection can be based on the following:

- History of previous and potentially repeatable problems during pregnancy
- Signs of potential premature parturition including premature mammary development, premature relaxation of ligaments around the tail head, premature vulvar elongation, vulvar discharge, urine staining beneath the vulva, or discharge found on the ventral aspect of the tail
- Current systemic compromise of the mare including infectious disease, metabolic disease, laminitis, colic
- Abnormalities detected during evaluation before the pregnancy such as cervical lacerations, vesicovaginal urine reflux, poor endometrial biopsy grade, metabolic or other systemic disease
- Abnormalities found during pregnancy moni-
toring. Monitoring can include physical examination, body condition score assessment, regular ultrasonographic assessment of the combined thickness of the uterus and placenta (CTUP), transabdominal ultrasonographic assessment of the fetus and placenta, hormonal measurements.

It is presumed that placentitis observed near the cervical star is due to pathogen ascent via the caudal reproductive tract and subsequently through the cervix. It stands to reason that routine transrectal ultrasonographic monitoring of this region can be helpful in attempting to achieve diagnosis of placentitis sufficiently early to make a difference. Similarly, in women, inflammatory diseases of the genital tract are among the most frequent diseases during pregnancy and are thought to account for 25% to 40% of preterm births, with the most frequent and serious ascending from the lower genital tract. It stands to reason that routine transrectal ultrasonographic monitoring of this region can be helpful in attempting to achieve diagnosis of placentitis sufficiently early to make a difference. Similarly, in women, inflammatory diseases of the genital tract are among the most frequent diseases during pregnancy and are thought to account for 25% to 40% of preterm births, with the most frequent and serious ascending from the lower genital tract.6

Renaudin et al (1997) published the evaluation of CTUP of 9 normal mares throughout gestation. Subsequently, evaluation of the CTUP has been incorporated into routine pregnancy monitoring programs (Table 2).6 In a field application of transrectal ultrasonographic assessment of the CTUP in 477 Thoroughbred mares on one farm in central Kentucky, placentitis was diagnosed in 3.1% of the mares. The abortion rate among mares with placentitis was 15.8%, with pregnancy loss occurring at an average of 62 days (range, 7 to 90 days) after detection and treatment onset. Of the nonaborting placentitis cases, 87% produced live foals, with a mean gestational length of 327 ± 2.23 days. The mean birth weight of live foals from affected mares (48.8 ± 1.56 kg) was not significantly different from foals born from unaffected mares (53.9 ± 0.28 kg). Foals that were born dead or died shortly after birth (not counted among live foals) were significantly smaller than surviving foals.7

Transabdominal ultrasonography can also be used to assess fetal health. Parameters that can be included to form a biophysical profile are fetal heart rate, fetal aortic diameter, fetal activity, fetal breathing movements, orbit diameter, tracheal diameter, stomach dimensions, kidney dimensions, gonadal dimensions, fetal fluid depth, uteroplacental thickness, and uteroplacental contact.8

Bucca (2011) has described the normal cervical dimensions of the pregnant mare.9 In humans, ultrasonographic cervical measurement has proved to be useful to detect patients at risk for preterm delivery regardless of parity or obstetric history.10

Maternal plasma total progestagen concentrations can be used to predict fetal health. The true concentrations of total progestagens being measured can vary substantially depending on the assay and antibody cross reactivity. Progestagen production involves the fetal adrenal; thus, progestagens can reflect fetal adrenocortical activity and stress. Rapid progestagen decline suggests severe fetal compromise. Progestagens at a level higher than normal are normally seen before spontaneous parturition at term and can also be seen in cases of placentitis or poor placental function. Progestagen levels that fail to normally rise before parturition suggest ergot alkaloid toxicity. In general, mares with high total progestagen concentrations are more likely to deliver live foals than those with low concentrations.11

Estrogen concentrations seem less useful than progestagens for predicting fetal health. Of the estrogens, estrone sulfate is the most frequently measured. High estrone sulfate levels (>100 ng/mL) indicate a viable fetus. Low estrone sulfate levels (<10 ng/mL) indicate fetal loss or a nonpregnant mare. Estrone sulfate may be transiently decreased with compromised pregnancy.11 The placenta is the sole source of circulating relaxin in the mare. As such, systemic relaxin concentrations could be used as a biochemical marker of placental function, fetal health, and a predictor of pregnancy outcome. Relaxin concentrations appear to be variable in individual mares and with pregnancy maintenance treatment. However, a commercially available relaxin assay, if one becomes

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<th>Month of Gestation</th>
<th>Mean CTUP, mm</th>
<th>95% Confidence Interval, mm</th>
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<tr>
<td>4</td>
<td>3.98</td>
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<td>5</td>
<td>3.58</td>
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<td>6</td>
<td>3.84</td>
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<td>7</td>
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<td>8</td>
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<td>12</td>
<td>9.52</td>
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From Renaudin et al, 1997.6
available, may prove to be useful to assess loss in placental function.\textsuperscript{12}

Practitioners vary with regard to readiness to obtain cervical or uterine cultures from pregnant mares, probably due to the concern of disrupting or inflaming the vulvar, vestibulovaginal, and cervical seals. If the procedure involves minimal disruption, for instance with the presence of discharge, microbial growth and antimicrobial sensitivity assessment can be helpful in constructing an antimicrobial treatment plan.

If pregnancy maintenance is deemed questionable, excellent client communication is necessary to manage everyone’s expectations regarding the outcome. Is the client prepared to witness an abortion? Given that the neonate and/or dam may be compromised, is there sufficient veterinary support available to provide immediate care? Who takes medical priority, the mare or the foal? Is the mare’s future reproductive soundness of utmost priority? Must the foal be an athlete? What are the financial constraints? If a problem has been identified before establishment of endometrial cups, is aggressive pursuit of pregnancy maintenance a better option than having another breeding opportunity that year?

2. Progesterone or Progestagens

In early gestation, progestins appear to be able to stand in for ovarian progesterone and prevent endotoxin- or prostaglandin-induced abortion. In later gestation, when, in the mare, numerous progestagens are present, the mechanism may include myometrial quiescence. Experimental models suggest that progestagen supplementation improves the odds of maintaining a placenta-compromised pregnancy to term. In two similar induced placentitis models in which mares were treated with trimethoprim sulfa (30 mg/kg PO BID) and pentoxifylline (8.5 mg/kg PO TID) with and without altrenogest (0.088 mg/kg PO SID), twice as many mares delivered live foals with altenogest treatment versus without altenogest treatment.\textsuperscript{13} In a study performed during the first trimester, alterenogest prevented abortion in 8 of 8 mares treated with cloprostenol, whereas control mares and 3 of 8 mares receiving progesterone aborted.\textsuperscript{14}

Once the pregnancy appears stable, many clinicians reduce the alterenogest dose to 0.044 mg/kg. Some clinicians prefer to use injectable progesterone (300 mg IM SID) or long-acting formulations. Monitoring fetal health and viability periodically during alterenogest treatment is recommended. Progestagen concentrations can be elevated in mares with compromised pregnancies, leading one to question the utility of progestagen supplementation in all cases.

Whether to discontinue altenogest before foaling (around 320 days of gestation) warrants discussion. In the placentitis model cited above, alterenogest treatment continued until parturition. In a study administering alterenogest (0.088 mg/kg PO SID) to 6 normal mares from 280 until parturition, with 7 mares serving as controls, stage II parturition was prolonged in alterenogest-treated mares, with signs of decreased neonatal viability including lower respiratory rate.\textsuperscript{15}

In humans, progesterone has a uterine-quiet effect, with the major mechanism of action in preventing preterm labor involving the cervix. Both synthetic progestin and natural progesterone treatment effectively lengthen the cervix. Clinical studies in humans have demonstrated that antiprogestins induce cervical ripening. Absence of progesterone at the cervical level results in the release of proinflammatory cytokines, with softening and effacement of the cervix but not necessarily uterine contractions. Progesterone treatment acting locally at the cervical level appears to control the release of proinflammatory cytokines and prevent extracellular matrix degradation of the cervix.\textsuperscript{3}

In a recent human study, the administration of vaginal progesterone gel to women with a sonographic short cervix in the mid-trimester is associated with a 45% reduction in the rate of preterm birth before 33 weeks of gestation and with improved neonatal outcomes.\textsuperscript{16} Studies using vaginal progesterone have shown higher endometrial progestesterone concentrations despite lower serum concentrations compared with more conventional intramuscular or oral progesterone treatment, suggesting a mechanism of direct transport between the vagina and uterus.\textsuperscript{3} This presents intriguing ideas for horses.

3. Anti-Inflammatory Agents

Pentoxifylline is a theobromine-derived, nonselective phosphodiesterase inhibitor. Phosphodiesterase inhibitors can decrease uterine activity by increasing intracellular c-AMP concentrations and thus lowering Ca\textsuperscript{2+} concentration. Pentoxifylline downregulates pro-inflammatory cytokines such as tumor necrosis factor-\(\alpha\), interleukin-6, and interferon-\(\gamma\). This drug also increases erythrocyte flexibility, fibrinolytic, and tissue plasminogen activator activity and inhibits platelet adhesion.\textsuperscript{17}

In mares, pentoxifylline has been shown to reach the allantoic fluid in normal pregnancy and in experimental placentitis models.\textsuperscript{18} Pentoxifylline has been detected in placental and fetal tissues at foaling, confirming its ability to cross the placenta and reach the foal.\textsuperscript{3} Additionally, a combination of alterenogest, antimicrobials, and pentoxifylline (8.5 mg/kg PO BID) resulted in an increased number of live foals in an induced placentitis study.\textsuperscript{13} In a study of women with imminent preterm labor, administration of pentoxifylline improved fetoplacental blood flow parameters and led to a significantly lower risk of neonatal complications.\textsuperscript{17}

Nonsteroidal anti-inflammatory agents such as flunixin meglumine (1.1 mg/kg) are commonly used as part of pregnancy maintenance therapy. Flunixin meglumine was not effective at preventing cloprostenol-induced abortion between 80 and...
150 days of gestation. Little additional research is available regarding its use for pregnancy maintenance.

Dexamethasone has been evaluated for induction of precocious fetal maturation. In a recent study in healthy Thoroughbred mares (n=10), mares received dexamethasone (100 mg IM SID) at 315, 316, and 317 days of gestation. Dexamethasone-treated mares had a significantly reduced gestation period. Foals were clinically mature with comparable body weights to controls, though with reduced crown–rump length. This treatment strategy can be useful in situations in which parturition must be induced in late gestation to preserve the mare’s health (eg, body wall hernia, prepubic tendon compromise, severe orthopedic compromise).

Antimicrobial treatment alone has been contrasted with antimicrobial treatment in conjunction with an anti-inflammatory (either dexamethasone or acetylsalicylic acid) in an induced placentitis model. In this study, 4 of 6 (67%) mares treated with trimethoprim sulfadiazine (30 mg/kg PO BID) alone delivered viable foals, whereas 8 of 11 (73%) mares treated with trimethoprim sulfadiazine and either dexamethasone (40 to 25 mg IV SID) or acetylsalicylic acid (50 mg/kg PO BID) delivered viable foals. Acetylsalicylic acid has the additional function of improving uterine and ovarian perfusion.

4. Antimicrobials

As mentioned previously, 34% of equine abortions or stillbirths were associated with feto-placental infection. Of these, 17.8% had an identified bacterial etiology. Antimicrobials are a critical component of bacterial placentitis treatment. Antimicrobials that have evidence of reaching allantoic fluid include penicillin G (22,000 units/kg IM BID), gentamicin (6.6 mg/kg IV SID), and trimethoprim sulfadiazine (15 to 30 mg/kg PO BID). Other antimicrobials are anecdotally used with effect.

In an experimental ascending placentitis model with β-Streptococcus, the introduced organism was able to be cultured from the uterus after foaling in both treated and untreated controls. The treated ponies received antimicrobials (trimethoprim sulfadiazine 30 mg/kg PO BID) continuously until parturition. This information suggests that antimicrobial therapy in pregnant mares with placentitis may need to be prolonged and weighed against side effects of long-term antimicrobial therapy.

Some clinicians and some farms routinely treat all mares with antimicrobials intermittently throughout gestation, presumably as a placentitis preventative. In a human parallel, in a survey of 38,151 newborn infants, 2698 (7.1%) had mothers with vulvovaginitis–bacterial vaginosis diagnosed and treated in early pregnancy. The rate of preterm births was 7.5% among these patients. In contrast, the rate of preterm births was 9.3% in babies born to mothers without recognized genital infections. Interestingly, the rate of preterm births was lower in babies born to mothers without recorded vulvovaginitis–bacterial vaginosis yet treated with antimicrobials (7.2% to 7.8%).

5. Tocolytics

Various tocolytics are used to suppress uterine contractility in women in preterm labor. In the mare, the tocolytic that has received the most attention is clenbuterol, a beta-sympathomimetic agent. In one study evaluating the efficacy of tocolysis (based on transrectal palpation of the uterus) of intravenous clenbuterol (300 μg) at various times through gestation in 4 mares found perceptible uterine relaxation lasting for up to 2 hours. Another study evaluated variable doses (0.6 mg IV, 1 mg IV, 1.5 mg IV) administered from 320 days to parturition and found no effect of treatment on outcome.

6. Oxygen

Oxygen therapy (10 to 15 L/min nasal insufflation) can be used in pregnant mares with compromised placentation to improve oxygen delivery to the fetus. This is remarkably easy to institute in a farm setting.

7. Acupuncture

Acupuncture is an important tool in equine reproduction. There are numerous studies supporting the use of acupuncture in achieving pregnancy. There are anecdotal reports regarding the efficacy of acupuncture for pregnancy maintenance; however, there are few controlled studies. Many studies focus on observation of tocolysis, though acupuncture treatment encompasses other measurable components. In one study in rats, acupuncture at LI-4, an important point for uterine quiescence, was found to suppress myometrial contractility in the face of oxytocin infusion. Another study demonstrated decreased expression of COX-2 in the myometrium of pregnant rats receiving acupuncture. In a small review evaluating acupuncture for inhibition of labor, 11 of 12 cases of preterm labor in women successfully carried to term.

8. Cervical Cerclage

Cervical cerclage involves placement of a suture within the musculature of the cervix that is tightened to obliterate the cervical lumen. Method of suture placement and efficacy of this procedure are more critically reviewed in mice than in mares. This procedure is typically used in cases of cervical incompetence that jeopardizes the pregnancy and is not sufficiently improved with progestagen therapy. Cervical cerclage has been used to prevent preterm births in women with a history indicating a risk of classical cervical insufficiency (eg, previous painless mid-trimester miscarriages or cervical surgery) or with mid-trimester dilatation of the internal os. Cerclage may worsen the outcome in patients with endocervical inflammation. Reports suggest that

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cerclage should only be offered to the 8% of women with a history of previous preterm birth (PTB) and within this the subgroup of patients with a cervical length <25 mm.3

Cervical cerclage is not commonly practiced in the mare. As cervical inflammation is present at the time of placentitis is diagnosed in advanced gestation, the optimum time for cerclage placement has passed. Also, if placed prophylactically before onset of placentitis, attentive monitoring for parturition is required to remove the suture before foaling.31

In reality, as practitioners rarely fully understand the mechanism of impending preterm birth in our equine patients. Thus, we rely on clinical experience, the wisdom of others, and clinical impressions. In the author’s practice, mares requiring pregnancy maintenance assistance usually receive pentoxifylline (if the budget allows), altrenogest (a client favorite), and antimicrobials if an infectious process is presumed or even possible. Anecdotal reports of the beneficial effects of aspirin exist in cases where marked pathological vascular changes have been reported. For repeated, idiopathic abortions, the author turns to acupuncture.

References